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10/538,231	11/25/2005	Ofer Mandelboim	2488.019	8744

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,231	MANDELBOIM ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-19 and 21-44* is/are pending in the application.

4a) Of the above claim(s) *6-18, 24-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,19 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant cancels claims 2 and 20..

Accordingly, group I, claims 1, 3-5, 19, 21-23, SEQ ID NO:4, species immunoglobulin, are examined in the instant application.

Withdrawn Rejection

The following rejection has been withdrawn: 1) 112, second paragraph, in view of the amendment, 2) 112, first paragragph, scope of enablement, in view of the amendment, and 3) 102, in view of the amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

A. Claims 1, 3-5 remain rejected under 35 U.S.C. 103(a) as being obvious over Pende et al, 1999 (J Exp Med, 190(10): 1505-1516, IDS of 02/13/06), in view of Mandelboim et al, Nature, February 2001, 409: 1055-1060, for reasons already of record in paper of 03/17/08.

The response asserts that Pende et al do not teach or suggest that NKp30, but not NKp46, is the main NK receptor that lyses tumor cells, and that Mandelboim et al do not teach or suggest that the conjugate NKp46-Fc induces or mediates lysis of target cells by NK cells.

The response asserts that Pende et al characterizes the role of NKp30 in tumor cell killing in a qualified manner: "NKp30 plays a central role in the killing of MEL15" (p. 1510, col.2); "Analysis of...other tumor target cells such as SMCC and A549...revealed a balanced contribution of NKp46 and NKp30 to the induction of cytotoxicity"; "NKp30 could exert an additive effect in the induction of NK-mediated cytotoxicity, not only with NKp46, but also with NKp44" (p. 1511, col. 1).

The response asserts that the lysis of target cells by NK cells in figure 1, b and c does not involved the conjugate NKp46-Ig. The response asserts as follows: Rather, Mandelboim et al teach that the conjugate NKp46-Ig (i.e. the extracellular domain of NKp46 fused to

immunoglobulin Fc) binds to haemagglutinin (HA) of influenza virus (IV) and to haemagglutinin-neuraminidase (HN) of parainfluenza virus, and that in a subset of NK cells recognition by NKp46 is required to lyse cells expressing the corresponding viral glycoproteins (see Abstract). More specifically, Mandelboim et al teaches that 721.221 cells infected with Sendai virus (SV) show increased binding to NKp46-Ig as compared to non-infected cells, that the effect is specific for NKp46 (see p. 1055, col. 2), that the binding is dependent on the viral HN, but that SV-infected 721.221 cells do not show an increased susceptibility to NK- mediated lysis by effector cells (see p. 1056, col.1). Mandelboim et al further teaches that 293T cells transfected with HN also show increased binding to NKp46-Ig, that the HN- transfected 292T cells are efficiently lysed by NK_GAL, an NK line derived from healthy donor peripheral blood lymphocytes, and that antibodies against NKp46-Ig or against HN inhibit the lysis (see p. 1056, col. 2). Notably, these lysis experiments do not involve the conjugate NKp46-Ig (see legend to Figure 1, b and c). Similarly, Mandelboim et al discloses that 1106mel cells infected with IV show enhanced binding to NKp46-Ig and increased lysis by NK GAL and by certain clones thereof, and that antibodies against NKp46-Ig or against HA inhibit the lysis (see p. 1056, col. 2-p. 1057, col. 1). Notably, these lysis experiments do not involve the conjugate NKp46-Ig (see legend to Figure 2, a- c). Finally, Mandelboim et al teaches that NKp46 directly interacts with the sialic acid binding site of HA (see p. 1058, col. 1-col. 2). Mandelboim et al concludes that NKp46 binds to target cells in two ways: first, through the interaction of NKp46-associated sialic acid with viral sialic acid receptors, and second, in a sialic acid -independent interaction with undefined cellular ligands (see p. 1058, col. 2).

The response asserts as follows: Further, and importantly, neither Mandelboim et al nor Pende et al teach or suggest that a conjugate comprising any NK molecule and an Ig molecule or Fc fragment thereof exhibits direct cytolytic activity on target tumor cells, as surprisingly disclosed in the subject application (see Examples 2 and 3). Rather, as detailed above, Pende et al shows only that endogenously expressed NKp30 must be exposed on fresh NK cells for those cells to be able to mediate cytotoxicity of certain target tumor cells. Mandelboim et al teaches that the conjugate NKp46-Ig binds to virally-infected cells or to cells expressing viral glycoproteins, but provides no teaching that the conjugate mediates lysis of such cells or any other targets of NK cells.

The response has been considered but is not found to be persuasive for the following reasons:

The Examiner agrees that Pende et al teach that NKp30 is the main KN receptor that involves in NK-mediated-lysis of only *certain* tumor cells (see Office action on page 8, last paragraph, item under the teaching of Pende et al), and that in some other tumor cells, NKp30 complements NKp46 and/or NKp44 for NK-mediated lysis of these tumor cells. The Examiner apologizes for any confusion when stating that NKp30 is the main NK receptor that involves in NK-mediated-lysis of tumor cells on page 9, third paragraph.

Further, Mandelboim et al teach that haemagglutinin (HN) can enhance lysis of virus infected target cells by NK cells, as well as activates NK cells directly, and that this activation is mediated by interaction with the triggerning receptor NKp46, as shown by inhibition of enhanced lysis of the target cells by NK GAL cells, after blocking of the interaction between the NKp49-Fc conjugate and HN molecules overexpressed on cell surface of the target cells (p.1057,

second column, second paragraph, and figure 1b and 1c, and figure 2). Thus, contrary to the response assertion, figure 1b and 1c and figure 2 in Mandelboim et al clearly indicate that enhanced lysis of target cells by NKGAL cells is required by the action of the conjugate of the extracellular domain of NKp46 and Fc (NKp46-Fc). One of which action is binding to the HN molecule on the target cells, as shown by inhibition of enhanced lysis by anti-NKp46 or anti-HN serum, which serum inhibits said binding (see for example, figure 1b, the graphs having the symbol 293/pca-svhn + anti-NK-p46 serum). Further, as shown in the title, Mandelboim et al conclude that recognition of the HN molecule on the target cells by NKp46 conjugate **activates lysis by human NK cells** (see title, abstract and figure 1 legend on page 1056). It is noted that it is expected that the conjugate NKp46-Fc binds and cross-link the NKp46 receptor via its Fc portion, in views of the teaching of Pende et al that an antibody or its Fc portion cross-links the receptor molecules NKp46 expressed on NK cell surface, which cross-linking of the receptors activates NK cells, resulting in triggering NK-mediated cytotoxicity of NK cells (p.1505, second column). Thus, it is not germane here whether or not Mandelboim et al do not teach that the binding of NKp46D2-Ig and NKp30-Ig conjugates to their unknown ligands on PC3 prostate cancer cells mediates the lysis of the cancer cells via macrophage-dependent lysis mechanism, and that in vitro killing of PC3 cells coated with the NKp30-Ig or NKp46D2-Ig conjugates by complement and NK cells was not observed, as asserted in the specification in Examples 2-3 on page 30, because the claims are composition claims, and are **not method claims**.

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to replace NKp46 in the NKp46-Fc conjugate taught by Mandelboim et al with another member of the NCR family, NKp30, for making NKp30-Fc conjugate for lysis of

target cancer cells by NK cells, in view that the conjugate NKp46-Fc by itself, without addition of a separate antibody, is required for enhanced lysis of target cells by a subset of NK cells, as taught by Mandelboim et al, and further in view that: 1) Crosslinking of NKp30 receptor is required to activate NK cell lysis of target tumor cells, as taught by Pende et al, and 2) NKp30, but not NKp46, is the main NK receptor that lyses some tumor cells, and also complements the action of NKp46 and/or NKp44 in some other tumor cells, as taught by Pende et al.

One would have a reasonable expectation that the NKp30-Fc conjugate would successfully trigger target cells lysis by NK cells, in view that crosslinking of NKp30 receptor by the Fc portion of a full length antibody is required to activate NK cell lysis of target tumor cells, as taught by Pende et al, which cross-linking would be expected to be successfully done by the Fc portion of the NKp30-Fc conjugate.

The response asserts that furthermore, neither Mandelboim et al nor Pende et al teach or suggest a polypeptide conjugate comprising NKp30 covalently attached to Ig or the Fc fragment of Ig, wherein the conjugate is in the form of a dimer.

The response has been considered but is not found to be persuasive for the following reasons:

One would have expected that it is the property of the NKp30-Fc conjugate to be in the form of a dimer, because it is the property of Fc fragment to cross-link molecules, in view of the teaching of Pende et al. It is noted that in a solution composition comprising NKp30-Fc, there are more than one single NKp30-Fc molecule.

The response further asserts as follows: It would not have been obvious to replace the signal peptide taught by Pende et al with a leader peptide and a restriction site for making and expressing the conjugate having the amino acid sequence of SEQ ID NO:4. The application discloses that SEQ ID NO:4 (also referred to in the application as NKp30-Ig) does not contain the complete NKp30 protein sequence but rather includes only the extracellular portion thereof (see page 27, lines 43-44 of the application as filed). Further, the application teaches that NKp30-Ig has activity in directly mediating lysis of cancer cells (Example 2), and in mediating tumor regression in experimental animals (Example 3). In contrast, Pende et al teaches cloning of a DNA sequence encoding the complete deduced NKp30 protein molecule, including the extracellular, transmembrane and cytoplasmic portions. However, Pende et al does not teach or suggest an isolated polypeptide conjugate in which a segment comprising- NKp30 or a fragment thereof is covalently attached to a segment comprising an Ig molecule or an Fc fragment of an Ig molecule, wherein the conjugate is in the form of a dimer, nor that such a conjugate could have direct cytolytic activity or target tumor cells, as surprisingly disclosed in the subject application.

The response has been considered but is not found to be persuasive for the following reasons:

It would have been obvious to use the extracelllular domain of NKp30 to make the NKp30-Fc conjugate, in view that in a conjugate of the same family member NKp46-Fc, the soluble NKp46 extracellular domain is used as taught by Mandelboim et al, and in view that Pende et al teaching that NKp30 belongs to the same Ig superfamily as NKp46 (p.1505), and that similar to NKp46, NKp30 protein contains a signal peptide and an extracellular domain, forming an Ig-like domain of the V type, which domain contains two glycosylation sites (p.1512, first

column, first paragraph). One would have a reasonable expectation of success in activation of NK-mediated lysis of target cells, because one would have expected that the extracellular NKp30-Fc conjugate would cross-link NKp30 receptors via its Fc portion and activates NK cell for lysis of target cells.

B. Claims 19, 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pende et al, 1999, J Exp Med, 190(10): 1505-1516, IDS of 02/13/06, in view of Mandelboim et al, Nature, February 2001, 409: 1055-1060 as applied to claims 1, 3-5 above, and further in view of Sukhatme et al (US 6,797,488), for reasons already of record in paper of 03/17/08.

The response asserts as follows:

Claims 19 and 21-23 as amended are dependent on claim 1. In accordance with the above explanations, claim 1 as amended is novel and non-obvious over the prior art including Pende et al and Mandelboim et al. Since base claim 1 is novel and non-obvious over the prior art, so too are claims 19 and 21-23 dependent therefrom, and may properly incorporate known subject matter.

The response has been considered but is not found to be persuasive for the following reasons:

Claim 1 is obvious over Pende et al and Mandelboim et al, supra.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the conjugate taught by Pende et al and Mandelboim et al with a pharmaceutically acceptable carrier, as taught by Sukhatme et al, for its storage.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
September 12, 2008

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643